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EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/528,569	GALY ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *1-6,and 9-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/19/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicants' timely election with traverse of Group V, Claims 7, 8, and 10, in the reply filed on 3 November 2006 is acknowledged.

Applicants traverse the lack of unity finding, stating that no adequate reasons and/or examples have been provided to support a conclusion of patentable distinctness between the identified groups or show that a search burden exists.

Applicants assert that Tuschl et al. do not teach or suggest siRNA against any gene.

Therefore, the corresponding special technical features required by PCT Rule 13.2 is present and the restriction should fall.

Applicants argue that a single general inventive concept is present in that all groups pertain to a method of obtaining and isolating a culture of antigen presenting cells wherein the expression of one or more of the genes is down-regulated comprising introducing an siRNA directed against said target genes.

Applicants cite M.P.E.P. in § 803, which states if a search and examination of an entire application can be made without a serious burden, the Examiner must examine it on the merits, even though it includes claims to distinct or independent inventions.

Applicants respectfully submit that a search of all of the claims would not impose a serious burden on the Office and point out that the European Patent Office searched all of the claims of the present application in one application.

Applicants' arguments have been fully considered but are not found persuasive.

The instant application is a National Stage Application filed under 35 USC §371 and subject to Unity of Invention practice, according to 37 CFR §1.499. See also MPEP §1850 and §1893.03(d). Applicants' citation of MPEP Chapter 800 is inappropriate to the instant case, as MPEP §800 is directed to Restriction Practice at it relates to U.S. Non-Provisional Applications filed under 35 USC §111(a). Applicants' attention is directed to the introductory paragraph of MPEP §801, where this is explicitly stated.

In National Stage Applications, burden of search and examination is not a factor for consideration in a determination of Unity of Invention. Similarly, the Examiner is not required to support any such findings of Lack of Unity with examples to show that the groups are independent or distinct.

The Examiner is only required to show that the groups lack the same or corresponding special technical feature—the contribution which each claimed invention, considered as a whole, makes over the prior art. In making this finding, it is proper for the Examiner to consider the special technical feature in terms of both novelty and inventive step (MPEP §1850, Section II).

As explained in the previous Communication, Narayanan et al. (US Patent 5591840) in view of Tuschl et al. render the special technical feature—an siRNA directed against the p50 subunit of NF-kappaB—obvious. Accordingly, unity of invention is lacking, *a posteori,* among Groups I–VI.

Applicants' contention that Tuschl et al. does not support an obviousness finding is not persuasive, since Tuschl et al. is considered to represent a complete blueprint for the design and manufacture of siRNA, teaching and exemplifying both methods and materials for designing, synthesizing, and using siRNAs against virtually any known gene. Tuschl et al. teach that

siRNAs are powerful reagents for inhibiting gene expression, and have utility as general research tools and therapeutic agents.

With regard to the search and examination performed by the European Patent Office, the instant Examiner is not bound by the findings or lack thereof of the international searching authority. The instant case is examined on its own merits.

With regard to Applicants' assertion that all groups pertain to a method of obtaining and isolating a culture of antigen presenting cells wherein the expression of one or more of the genes is down-regulated comprising introducing an siRNA directed against said target genes, this concept or feature is disclosed and/or suggested by the combination of references, Foxwell et al., Tuschl et al., and Bass, as explained below.

The requirement is still deemed proper and is therefore made FINAL.

Status of the application

Claims 1–11 are pending. Claims 1-6, 9, 10, and 11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claim 10 is withdrawn in view of Applicants' amendment to the claim, submitted with the response filed on 3 November 2006, which changes the dependency of claim 10 form claim 1 to claim 9. Claim 9 belongs to non-elected Group VI, which was found to lack unity with elected Group V. Accordingly, a search and examination of claim 10, as now amended, would involve a search and examination of the method of non-elected Group VI.

Claims 7 and 8 are examined herein.

Specification

The specification is objected to because it fails to comply with *37 CFR 1.74* since it lacks Brief Descriptions of the Drawings: Figures 1–10.

Appropriate correction is required. However, Applicants are specifically advised of the prohibition against adding new matter to the specification (35 USC §132).

> *37 CFR 1.74 Reference to drawings.*
> When there are drawings, there shall be a brief description of the several views of the drawings and the detailed description of the invention shall refer to the different views by specifying the numbers of the figures, and to the different parts by use of reference letters or numerals (preferably the latter).

Claim Objections

Claims 7 and 8 are objected to because they depend from a withdrawn claim: claim 1. Amending the claims to include all the limitations of claim 1 would overcome this objection, keeping in mind that the elected invention is drawn to "An antigen-presenting cell."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foxwell et al. (U.S. Patent Application Publication 2003/0153518 A1); Tuschl et al. (US Patent Application Publication 2004/0259247 A1); and Bass (2001) *Nature* 411:428-429.

Foxwell et al. teach antisense oligonucleotides targeted to the gene encoding the p50 subunit of NF-κB for inhibiting p50 expression in antigen-presenting cells such as dendritic cells (paragraphs 40-43, 55-58, and 123, for example).

Foxwell et al. teach that NF-κB can be used as a target to induce or modulate an immune response in antigen-presenting cells (paragraphs 14-18, for example).

Foxwell et al. teach that inhibiting p50 expression and, thereby, NF-κB activity may be used to modulate immune responses in cells. Foxwell et al. teach, for example, that their invention provides for a method of inhibiting antigen presentation or inducing an anergic response in a mammal comprising administering a pharmaceutically-effective dose of an inhibitor of NF-κB (paragraph 22). At paragraph 34, Foxwell et al. teach that NF-κB inhibitors may be used as medicaments to induce an anergic response, to inhibit the rejection of transplanted tissue, or as anti-autoimmune disease agents or to treat allergy.

Foxwell et al. describe several modes of delivery and treatment, teaching that dendritic cells may be manipulated *ex vivo* and treated with an NF-κB inhibitor such as an antisense nucleic acid or construct expressing an antisense nucleic acid, and then reintroduced into the patient (paragraph 125, for example). Foxwell et al. teach that dendritic cells may be cultured and/or enriched under various conditions and formulated for reinfusion into a patient. For example, Foxwell et al. teach that the ex vivo expansion of autologous dendritic cells from patients, loading with a peptide antigen and reinfusion as adoptive immunotherapy, is described in, for example, WO/00/26249.

Accordingly, Foxwell et al. teach the methods, materials, and utilities of inhibiting p50 and other NF-κB genes in antigen-presenting, dendritic cells for immune response modulation, comprising the use of antisense oligonucleotides for gene specific inhibition of NF-κB protein subunits, as well as various pharmaceutical methods thereof, including the ex vivo and in vivo targeting of dendritic cells with antisense oligonucleotides to reduce levels of NF-κB in these antigen-presenting cells.

Foxwell et al. do not teach using siRNA to inhibit NF-κB expression in dendritic cells or any other antigen-presenting cell.

Tuschl et al. (US 2004/0259247) teach methods and materials for making and using short, double-stranded, interfering RNA molecules for mediating target-specific gene silencing via RNA interference (RNAi) against virtually any known gene in mammalian cells.

It is taught that double-stranded RNA molecules 19-25 nucleotides in length have RNAi activity and may trigger the specific degradation of homologous RNAs within the region of identity with the dsRNA (paragraphs 5, 7, 11, and 17 for example). Tuschl et al. teach that siRNA duplexes are preferably composed of 21-nt antisense siRNAs and should be selected to form a 19-bp double helix with 2-nt 3' overhanging ends (paragraphs 9, 11, 179).

Tuschl et al. teach that dsRNA molecules may be chemically or enzymatically synthesized using methods known in the art (paragraphs 20-24, 97, 141). Tuschl et al. teach that dsRNAs may be formulated in pharmaceutically acceptable compositions for use in therapeutic applications (paragraph 31-33).

In summary, the Tuschl et al. reference is considered to be a complete blueprint for the design, synthesis, and use of short interfering, double-stranded RNA, in modified or unmodified forms, against any desired target gene (see siRNA User Guide, for example, at paragraphs 178-181). The reference contains detailed descriptions and several examples typfying the use of siRNA in cell culture, and the Application Publication expressly suggests the use of siRNA *in vivo* for use in therapeutic and clinical settings (paragraphs 31-36).

Importantly, Tuschl et al. also compare siRNA methodology to that of antisense and ribozyme techniques for inhibiting gene expression. At paragraph 148, for example, Tuschl et al.

state that siRNAs are extraordinarily powerful reagents for mediating gene silencing and that siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments. At paragraph 137, Tusch et al. state that the remarkable finding that synthetic 21 and 22 nt siRNA duplexes can be used for efficient mRNA degradation provides new tools for sequence-specific regulation of gene expression in functional genomics as well as biomedical studies. The siRNAs may be effective in mammalian systems where long dsRNAs cannot be used due to the activation of the PKR response. As such, the siRNA duplexes represent a new alternative to antisense or ribozyme therapeutics

Bass teaches that, like some antisense oligonucleotides, which trigger RNase H-catalyzed cleavage of their targets, siRNAs trigger the degradation of complementary messenger RNAs (page 428 and Fig. 1). A general outline of the RNAi mechanism is taught, showing how siRNA-mediated RNAi may be used to interfere with gene expression using siRNAs directed against specific mRNA sequences (Fig. 1). Bass teaches that RNAi has repeatedly proven itself to be more robust that antisense techniques: it works more often, and typically decreases expression of a gene to lower levels, or eliminates it entirely. Furthermore, siRNAs are effective at concentrations that are several orders of magnitude below the concentrations typically used in antisense experiments.

Thus, the prior art teaches, in general, that siRNAs and antisense oligonucleotides can be used to produce the same effect, albeit with different potencies and by different biochemical mechanisms. siRNAs and antisense oligos can both be used to inhibit gene expression *in vivo* or *in vitro*, via mRNA degradation or translation attenuation, and, thus, both types of nucleic acids

may be used to prevent the expression of a gene in a cell. For example, Bass teaches that antisense RNA is another technique to prevent the expression of particular genes (page 429). Thus, in this sense, siRNAs and antisense oligos are art-recognized equivalents that may be used for the same purpose: reducing or inhibiting gene expression. (See for example MPEP §2144.06, SUBSTITUTING EQUIVALENTS KNOWN FOR THE SAME PURPOSE.)

Nevertheless, as explained above, siRNAs possess certain advantages over antisense oligos, which would motivate one of ordinary skill in the art to select siRNAs over antisense oligos to more efficiently block and/or reduce the expression of any given target gene, particularly a gene known to be involved in cancer.

Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to use dsRNAs, or more specifically, siRNAs, as taught by Tuschl et al. and Bass, for inhibition of NF-κB expression, specifically p50 expression for the reasons taught and suggested by Foxwell et al. to modulate immune responses in antigen presenting cells.

One would have been motivated to use siRNAs in place of antisense oligonucleotides in the methods of Foxwell et al. given that Tuschl et al. and Bass teach that siRNAs are, in general, more potent, and therefore more effective inhibitors of gene expression.

Finally, one would have a reasonable expectation of success given that Foxwell et al. teach and suggest methods for manipulating antigen-presenting cells, specifically dendritic cells, in culture and ex vivo and treating such cells with NF-κB antagonists such as antisense oligonucleotides, and teach that the cDNA sequence for p50 is known (paragraph 10) and given that Tuschl et al. teach methods and materials for making and using siRNAs against any known target sequence and that the mechanism of RNAi, as taught by Tuschl et al. and Bass primarily

requires a knowledge of the target gene sequence to design putative siRNA reagents using standard solid phase synthesis techniques.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LVW
Examiner, Art Unit 1635
November 27, 2006

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER